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To: **Dr. Cathy Ellis** **Date:** January 15, 1998

From: **Richard Carchman**

Subject: **Preliminary comments on JAMA article 14 Jan. 1998**

I have just received a copy of the article entitled ***Cigarette Smoking and Progression of Atherosclerosis*** published in the Journal of the American Medical Association (JAMA) 279, No. 2, pp. 119-124 authored by Howard et al. This published study represents a partial analysis derived from the Atherosclerosis Risk in Communities (ARIC) population previously described (Amer. J. Epid., 129, No. 4, pp. 682-702, 1989). ARIC is a multicenter population based investigation of approximately 16,000 individuals (male and female) examined/questioned twice between 1987-1989 in four centers (i.e. Minnesota, Maryland, Massachusetts, North Carolina). The study population was divided into five groups. Smoking history was obtained by self report. Smokers were then further subdivided as current or past (>100 cigarettes in the past). Never smokers not characterized further. "Exposure" to environmental tobacco smoke (ETS) for past and never smokers was determined by answering the following question: "During the past year, about how many hours/week, on average, were you in close contact with people when they were smoking? For example, in your home, in a car, at work, or other close quarters." Never and past smokers were classified as exposed to ETS if they reported contact with smokers >1 hour/week. The authors do not report on the use of any objective measures for assessing the validity of recent current or recent past smoking status (e.g., cotinine). Since smoking misclassification is not evaluated, this will impact the authors' inferences. The authors should have evaluated spousal smoking status as it should also impact their analyses. The authors' categorization of ETS exposure based on the question used is so limited as to be useless as a metameter for ETS exposure. At best the question provides some insight into past events (one year) on duration events only. Exposure contains at least one other parameter, i.e., intensity. It is at a minimum the product of intensity and duration derived from objective measurements that are robust enough to even approach the use of the category ETS exposed.

This paper utilizes an ultrasound technique that measures blood vessel wall thickness that according to the authors is a surrogate for atherosclerosis. 'Baseline' measurements were taken in 1987 (Table 1) and then again three years (1989) later and progression of events recorded (Table 1). Judging from the baseline and progression data presented in Table 1 for the different groups evaluated no meaningful group differences are apparent. The blood vessel thickness measured are derived from the common carotid artery only. Other blood vessel measurements were not used because of missing data and greater variability. The evaluation of the ultrasound information were carried out by individuals who were blinded to the patients groupings (e.g., smoker versus non-smoker). The authors state that this process produces a single index of atherosclerosis with improved precision (no data provided). The inclusion of males and females in the measurement of this one blood vessel requires the reader to be aware of different blood vessels effects reported for atherosclerosis as a function of gender. The authors have an ability to

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address this question with the data they already have. This type of analysis could be relevant as to the generalizability of this study and or the validity of the authors inferences.

Surprisingly, based on the baseline and progression data provided in Table 1, the authors continued their analysis (see Table 2). The further analyses presented in Table 2 is divided into two sections--section 1 looks at the five groups utilizing three different mathematical models that adjust for other reported risk factors for atherosclerosis. Each model according to the authors have relatively different degrees of sophistication. The authors point out (p.121) "The need for covariant adjustment is supported by the dramatic differences in the prevalence of cardiovascular risk factors and lifestyle variables. Because of these differences in risk factors across smoking categories, the comparison of unadjusted atherosclerosis progression rates across the smoking strata (which shows increased progression rates with increased cigarette smoke exposure) should be made cautiously." It appears from how the authors relate the data derived from their mathematical models that this legitimate concern was abandoned in the comments section of their paper. Furthermore, the nature of the covariants examined in this paper requires some comment. The covariants for cardiovascular disease included:

- hypertension--based on blood pressure measurements or self reported use of antihypertensives;
- LDL cholesterol-measurements;
- Diabetes--blood glucose measurements or self reported use of antidiabetic medications or self report per se;
- Fat intake--by questionnaire; physical activity--by questionnaire;
- Alcohol use--self report; and
- Body mass index--determined objectively.

Individual exclusion/inclusion criteria for this analysis eliminated >5000 subjects from their evaluations. The covariant risk factors used are a mix of quantitative, qualitative, subjective, and objective determinations. Why other covariant risk factors were not incorporated nor the impact of combining such a mixed approach to the risk factors used is not discussed by the authors is unfortunate. It appears that this aspect of their evaluations leaves the serious reader further questioning the real scientific value of their analyses, inferences, and conclusions. The second section of Table 2 groups the comparisons to evaluate the ETS effect, past versus never smokers and current versus past smokers, for each of the three mathematical models used. It is important to note that comparing the outcomes derived from model 3 with models 1 and 2 demonstrates the complexity of these analyses e.g., the ETS effect is $\geq$ than the current and past smoker effect for models 1 and 2, but not for model 3. This suggests the following possibilities:

(1) the very limited value of the covariants used in models 1 and 2, and
(2) that even the more complex model (#3) is still too restrictive in that other important covariants (confounders) remain to be evaluated.

A significant point as to the relevance of Table 2 is the presentation of the data from Table 2 (model #3) in Fig. 1 (p. 122). Unlike the authors' conclusions derived from section 2 (Table 2), Fig. 1 draws the reader to come to a different series of conclusions and further questions the basis

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for how the authors aggregated their data for analysis in Table 2 (Section 2). Comparing never smokers with and without ETS "exposure" or past smokers with and without ETS "exposure" no significant differences ("ETS" effect) are found as it might relate to the progression end point. Similarly, there is no statistically significant difference between current smokers and past smokers "exposed" to ETS (Fig. 1). These conclusions are in stark contrast to what the authors conclude and yet this discrepancy is not addressed.

The authors indicate in the text (p. 122) that subjects (never and past smokers) were asked to assess the number of hours of ETS "exposure" and this information was then correlated ("dose-response") with the progression rate. The authors conclude that "there was no evidence of a dose response." Aside from the fact that dose was never determined, the failure to establish a correlation between "dose" and effect (progression) undermines the biological plausibility of the association. The authors try to minimize this discrepancy (p. 123) by undermining the validity of the use of the ETS "exposure" to quantify the number of hours/weeks exposed.

Overall, I found the date, its analyses, and the authors' conclusions weak and contradictory. I believe that all one would be able to say is that there may be certain associations between "exposures" and the endpoint measured. Causality arguments are at best premature; the use of imprecise data collection methods, less than robust analyses, and the inclusion(s) of highly speculative mechanistic scenarios is scientifically unjustified.

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